REMARKS

It is respectfully requested that this application be reconsidered in view of the following remarks.

Amendments

Obvious errors were corrected in the specification as follows:

in the bridging paragraph at pages 8-9;

in the bridging paragraph at pages 16-17;

in the bridging paragraph at pages 23-24;

in the paragraph beginning at line 8 at page 24;

in the paragraph beginning at line 15 at page 29;

in the bridging paragraph at pages 30-31;

in the bridging paragraph at pages 65-66;

in the bridging paragraph at pages 68-69;

in the bridging paragraph at pages 75-76; and

in the paragraph beginning at line 30 at page 84.

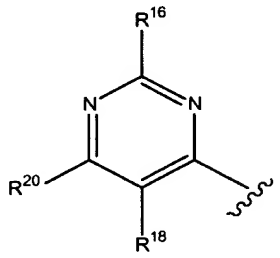
These amendments have been made in accordance with 37 C.F.R. §1.121 as amended on November 7, 2000. As required, attached hereto is an appendix illustrating the changes made to the specification.

Entry of these amendments is earnestly solicited.

Election of Species Requirement

The Office Action states that Claims 1-26 are generic to a plurality of disclosed patentably distinct species comprising compounds of formulas I, IIa, IIb, IIc, IId and IIe and, therefore, an election of species was required to provide for specific values of ring A.

In response to this requirement, Applicants elect, without traverse, the ring system which is found in formula IIc and is represented as follows:

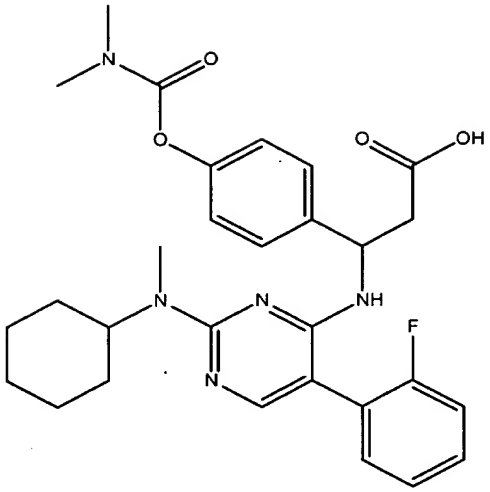


Applicants submit that the above election is sufficient to respond to the election of species requirement set forth by the Office Action, in as much as this election provides specific values for ring A. Further, Applicants believe that Claims 1-26 read on the above elected ring.

If a specific compound is required to be responsive to this election of species requirement, then Applicants elect, without traverse, the following single disclosed species:

(R,S)-3-(5-(2-Fluorophenyl)-2-(N-cyclohexyl-N-methylamino)-pyrimidin-4-ylamino)-3-(4-(dimethylaminocarbonyl)oxyphenyl)propanoic acid.

This compound is represented by the formula:



and is disclosed in Example 3 of the specification (p. 102). Applicants believe that Claims 1-14 and 24-26 read on this compound.

Early examination on the merits is requested.

Respectfully submitted,

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Date: August 7, 2002

Attachment to Reply and Amendment dated August 7, 2002

Marked-up Copy

The following amendments were requested to the specification:

The bridging paragraph at pages 8-9 was amended as follows:

--B is a group wherein W, together with -C(=Z)NR^2-, forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and -SO_n- (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of [with one or two substituent(s) selected from the group consisting of] hydrogen, hydroxy, alkoxy, substituted alkoxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, aminoacyl, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, alkylene dioxy, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;--

The bridging paragraph at pages 16-17 was amended as follows:

--(a) a group wherein W, together with -C(=Z)NR^2- where Z is -O-, forms an unsaturated heterocyclic group containing 3 or 4 carbon atoms and 0 or 1 additional nitrogen atom[s] and further [the] wherein the unsaturated heterocyclic group is optionally substituted, in addition to the R^2 group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino. Preferably B is a 2-pyridone, (e.g., 2-pyridon-3-yl, 2-pyridon-4-yl, etc.,) or 6-pyrimidone (e.g., 6-pyrimidon-5-yl, etc.,) that is optionally substituted in addition to the R^2 group[,] with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino, more preferably methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy (wherein the methyl, ethyl, propyl, butyl, and allyl group in said methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy may be optionally substituted with [one, two, or three] 1 to 3 substituents selected from the group consisting of hydroxy, alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, halo, alkylamino, dialkylamino, amino, aminoacyl, preferably, hydroxy, methoxy, ethoxy, methylthio, methylsulfane, methylsulfone, fluoro, methylamino, dimehtylamino, amino, and acetylamino), chloro, bromo, hydroxy, methylamino, or dimethylamino. More preferably in the above rings R^2 is alkyl, preferably methyl; or--

The bridging paragraph at pages 23-24 was amended as follows:

--B is a group wherein W, together with -C(=Z)NR^2-, forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and -SO_n- (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further

wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of [with one or two substituent(s) selected from the group consisting of] hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-Nalkylamino, alkylene dioxy, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl; and

[and] enantiomers, diasteromers and pharmaceutically acceptable salts thereof.--

The paragraph beginning at line 8 at page 24 was amended as follows:

--In the above compounds III(a-e), B is either:

(a) a group wherein W, together with $-C(=Z)NR^2-$ where Z is -O-, forms an unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms and further [the] wherein the unsaturated heterocyclic group is optionally substituted, in addition to the R^2 group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino. Preferably B is 2-pyridone, (e.g., 2-pyridon-3-yl, 2-pyridon-4-yl, etc.,) or 6-pyrimidone (e.g., 6-pyrimidon-5-yl, etc.,) that is optionally substituted, in addition to the R^2 group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino, preferably methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy (wherein the methyl, ethyl, propyl, butyl, and allyl group in said methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy may be optionally

substituted with [one, two, or three] 1 to 3 substituents selected from the group consisting of hydroxy, alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, halo, alkylamino, dialkylamino, amino, aminoacyl, preferably, hydroxy, methoxy, ethoxy, methylthio, methylsulfane, methylsulfone, fluoro, methylamino, dimethylamino, amino, and acetylamino), chloro, bromo, hydroxy, methylamino, or dimethylamino. More preferably in the above rings R^2 is alkyl, preferably methyl; or--

The paragraph beginning at line 15 at page 29 was amended as follows:

--X is hydroxyl; [and]

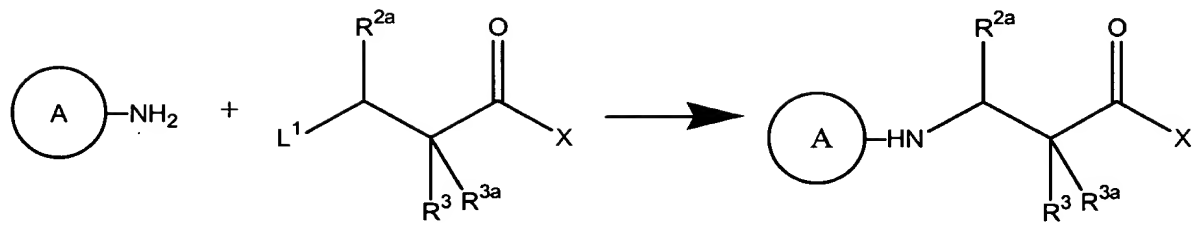
The bridging paragraph at pages 30-31 was amended as follows:

--The compounds and pharmaceutical compositions of this invention are useful for treating disease conditions mediated by VLA-4 or [leucocyte] leukocyte adhesion. Such disease conditions include[,] by way of example, asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermititis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.--

The bridging paragraph at pages 65-66 was amended as follows:

--In another preferred embodiment, compounds of this invention may be prepared by displacement of a leaving group as shown in scheme 2:

Scheme 2



7 **8** **I**

where [R^2] R^{2a}, R^3, R^{3a} and X are as defined herein; A is heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic containing two nitrogen atoms in the heteroaryl or heterocyclic ring; and L^1 is a leaving group, such as chloro, bromo, iodo, sulfonate ester and the like.--

The bridging paragraph at pages 68-69 was amended as follows:

--A compound of formula **(I)** can also be prepared by first reacting **10** wherein A is as defined herein, X^3 is halogen, such as chloro, bromo or iodo (preferably iodo) with a 3-aminopropionic acid derivative of formula **13** wherein R^y is a suitable group that can be converted to a R^{2a} group which is defined in the Summary of the Invention. Initially, reaction of a compound of formula **10** with a compound of formula **13** under the reaction conditions described above provides an intermediate of formula **14** which is then converted to a compound of formula **(I)**. It will be well recognized by those skilled in the art that the choice of the R^y substituent will depend on the type of R^{2a} group desired in compound **(I)**. For example, if a compound of [Formula] formula **(I)** [is] where R^{2a} is -Ar^1-R^9 wherein Ar^1 is phenyl and R^9 is a carbamoxy group is desired, then it can be prepared by first coupling **10** with a (R)-3-amino-3-(4-(*tert*-butyldimethyl-siloxy)phenyl)propanoic acid ethyl ester to give N-substituted-(4-(*tert*-butyldimethyl-siloxy)phenyl)propanoic acid ethyl ester which

upon deprotection of the hydroxy group provides N-substituted-(4-hydroxyphenyl)propanoic acid ethyl ester. N-Substituted-(4-hydroxyphenyl)propanoic acid ethyl ester can then be contacted with about 1.0 to 1.2 equivalents of a chloroformate in an inert diluent, such as dichloromehtane, at a temperature ranging from -25°C to about 0°C for about 0.5 to about 2.0 hours. Treatment of the resulting carbonate with an excess, preferably about 2 to about 5 equivalents, of a trialkylamine, such as triethylamine, for about 0.5 to about 2.0 hours, followed by about 1.0 to about 1.5 equivalents of a primary or secondary amine provides the carbamate. Examples of amines suitable for [using] use in this reaction include, but are not limited to, piperazine, 1-methylpiperazine, 1-acetylpiperazine, morpholine, thiomorpholine, pyrrolidine, piperidine and the like.--

The bridging paragraph at pages 75-76 was amended as follows:

--Alternatively, a hydroxyl group present on a substiuent of a compound of formula **I-IV** or an intermediate thereof can be [*O*-alkylating] O-alkylated using the Mitsunobu reaction. In this reaction, an alcohol, such as 3-(N,N-dimethylamino)-1-propanol [and the like], is reacted with about 1.0 to about 1.3 equivalents of triphenylphosphine and about 1.0 to about 1.3 equivalents of diethyl asodicarboxylate in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about -10°C to about 5°C for about 0.25 to about 1 hour. About 1.0 to about 1.3 equivalents of a hydroxy compound, such as N-*tert*-butyltyrosine methyl ester, is then added and the reaction mixture is stirred at a temperature of about 0°C to about 30°C for about 2 to about 48 hours to provide the [*O*-alkylated] O-alkylated product.--

The paragraph beginning at line 30 at page 84 was amended as follows:

--The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinyl-pyrrolidone is mixed with the resultant powders, which are then passed through a No. 16 mesh U.S. sieve. The granules

so produced are dried at 50°C to 60°C and passed through a No. 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing [150 mg] 120 mg.--